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OPTIMIZING CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE PATIENTS BY MEASURING TRANSIENT CHANGES IN SINUS RATE DURING PACING

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Abstract-**To optimize cardiac resynchronization therapy (CRT) for chronic heart failure (CHF) patients, acute studies show that left ventricular pacing site and atrio-ventricular (AV) delay can be individualized to maximize aortic pulse pressure (PP) increase. In the normal patient it is known that atrial cycle length (ACL) increases as PP increases via the baroreceptor reflex. Therefore, we evaluated another parameter for optimization of pacing parameters – transient ACL, or inversely, sinus heart rate. In a retrospective study, 29 CHF patients, acutely implanted to measure ACL and aortic PP, each received atrial-triggered ventricular pacing in 15 different randomized combinations of 3 pacing sites and 5 AV delays. Each trial contained 15 intrinsic beats (no pacing) and 5 paced beats; PP and ACL changes with pacing were averaged over the 5 trials. The pacing combination with maximum ACL increase was hypothesized to be statistically related to maximum PP increase. For patients responding to pacing therapy (N = 20), the ACL algorithm predicted optimal or near-optimal (PP increase > 75% of optimal) pacing combinations for most of these patients (85%) and predicted combinations yielding 50-75% of optimal for the rest (15%). This paper describes an algorithm for optimizing PP response via transient ACL measurements. The ACL algorithm may allow rapid and minimally invasive optimization of pacing site and AV delay for CRT in CHF patients.**

Keywords **- Cardiac pacing, chronic heart failure, baroreceptor reflex, hemodynamics, left ventricular function, cycle length, cardiac resynchronization therapy**

I. INTRODUCTION

Over the past decade, several pioneering studies have investigated the possible use of pacing therapy to treat patients with chronic heart failure (CHF) and ventricular conduction delay [1,2]. In these studies, Cardiac Resynchronization Therapy (CRT) has been shown to improve acute hemodynamic performance via left ventricular (LV) or bi-ventricular (BV) pacing. To date, CRT for CHF patients [3] has been performed using empiric settings, invasive pressure measurements, or cumbersome echocardiographic methods to guide device programming since little data exist to prospectively guide selection of optimal parameters.

The acute optimum settings are the combination of pacing site(s) and atrio-ventricular (AV) delay that maximize hemodynamic performance. Several optimization approaches utilize direct measurement of hemodynamic parameters. One approach [3] optimizes left heart AV timing based on Doppler recordings of aortic or pulmonic flow velocity. Another approach [4] measures time-varying ventricular volume from a conductance catheter.

Acute studies that directly measure intracardiac pressures [4, 5-9] have shown hemodynamic improvement with resynchronization therapy [5,6,7] and highlight that hemodynamic response is dependent on pacing site and AV delay [8, 9].

Pulse pressure (PP) obtained with invasive catheterization techniques is an accepted optimization variable since a small increase in PP is associated with a large increase in stroke volume [4]. Acute PP response has limited application to pacemaker therapy in CHF patients since aortic pressure sensors for chronic implants are not available. PP, however, is physiologically related to atrial cycle length (ACL) via the baroreceptor reflex mechanism, a negative feedback control loop that uses sinus heart rate, or cycle length, to maintain a stable arterial pressure [10]. The objective of this study was to retrospectively test if changes in ACL observed during transient changes in aortic PP can predict which pacing site and AV delay maximizes PP increase in CHF patients that are candidates for CRT.

II. METHODOLOGY

Patient Description

We investigated a patient subgroup from the PATH-CHF clinical trial. The PATH-CHF main inclusion criteria [3] were: NYHA class III to IV with severe LV systolic dysfunction, long PR due to first-degree heart block, wide QRS complex (≥ 120 ms), normal sinus rhythm, and no history of arrhythmia. The PATH-CHF main exclusion criteria [3] were: recent atrial or ventricular tachyarrythmia, recent myocardial infarction, recent or pending artery revascularization, severe valve disease, intravenous inotrope dependence, or indications for pacemaker implantation.

Additional exclusion criteria for this analysis were frequent premature atrial and ventricular contractions and excessive noise in the ACL data. Twenty-nine PATH-CHF patients had reliable ACL data. Six patients were ischemic and 23 were non-ischemic. The mean LV ejection fraction was 21% with a range of 7% to 40%. The clinical characteristics of these 29 patients did not differ significantly from the overall PATH-CHF population.

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Abstract

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Data Collection

Pressure catheters and pacing leads were connected to a custom external pacing computer (FlexStim™, Guidant Corp., St. Paul, MN) to acquire hemodynamic and electrocardiographic signals and execute a prescribed pacing protocol [3, 11] in which patients had general anesthesia. Chronic pacing leads were implanted with positive fixation leads in the right atrial appendage and right ventricle (RV), and an epicardial lead was attached to the LV surface via a limited thoracotomy. The LV pacing site was apical or midlateral. One 8F dual-transducer pressure catheter measured aortic PP and LV pressure. In addition, a standard 12-lead surface ECG was recorded.

Raw pressure and electrogram data were recorded on a digital tape recorder with 16-bit resolution at a 12,000-Hz sampling rate. Data were anti-alias filtered and downsampled to 500 Hz for offline analysis. The right atrial electrogram was used to determine ACL. Maximum systolic aortic pressure minus end-diastolic aortic pressure determined PP. The maximum of leads II, V1, and V6, measured automatically and validated manually by two independent observers, determined QRS duration.

Pacing Treatments

The FlexStim™ pacing protocol measures the immediate pacing effects and accounts for baseline drift. The RV, LV, or BV were stimulated in a VDD mode (atrial sense followed by ventricular pacing at one of 5 predetermined AV delays). The AV delays were preset percentages (0, 25, 50, 75, and 100) of intrinsic AV minus 30 ms. A trial for one of the 15 particular combinations of pacing site and AV delay consisted of 5 paced beats followed by 15 intrinsic beats. For the first iteration of 15 trials, each combination occurred only once. Next, the combinations were randomized again for the second iteration of 15 trials, etc., until 5 iterations were completed. The test duration was approximately 30 minutes.

ACL Optimization Algorithm

ACL data were smoothed with a moving 11-point Blackman window. The ACL for the paced period minus the ACL for the preceding intrinsic period, averaged over all 5 trials, determined each pacing combination's ACL change. The combination with maximum ACL increase was the predicted optimum pacing combination - the combination predicted to yield the maximum PP increase.

ACL Algorithm Validation

Each combination's actual PP change was determined as the invasively-measured PP for the paced period minus the PP for the preceding intrinsic period, averaged over all 5 trials. The combination with the maximum PP increase was the actual optimum pacing combination, the gold standard used to test the ACL algorithm predictions.

QRS Width Criterion

The ACL optimization algorithm was used with patients whose PP responds to CRT (Pacing Responders_{PP}). However, if the maximum PP change was less than a 5% increase over the intrinsic PP, the patient was defined to be a Pacing $\text{Non-Responder}_{PP}$. A surface-ECG QRS width divided the patients into Pacing Responders_{QRS} (QRS width ≥ 150 ms) and Pacing $\text{Non-Responders}_{QRS}$ (QRS width < 150 ms). This criterion is a good approximate threshold for separating Pacing Responder_{PP} from Pacing $\text{Non-Responder}_{PP}$ [4, 9]. The ACL optimization algorithm was next applied to the Pacing Responders_{QRS}.

III. Results

Optimum Pacing Combination Selection

Results of the 15 different pacing combinations on ACL and PP are presented for one representative patient in Fig. 1. The arrow points to the pacing combination with maximum ACL increase. This combination, as selected by the maximum ACL increase, had a measured PP increase that was more than 85% of the maximum PP increase achieved in this patient.

Effectiveness of the ACL Optimization Algorithm for Various Patient Groups

In Fig. 2, the PP change for the predicted optimum combination (the ordinate) occurred at the combination with maximum ACL increase. The PP change for the actual optimum combination (the abscissa) occurred at the combination with the maximum PP increase.

Three subgroups of patients are present:

1) A group of 20 patients (69%) where CRT increased PP, assessed by invasive pressure measurement. These patients (filled circles) are both Pacing Responders_{PP} (gold standard) and Pacing Responders_{QRS}. Ten patients were on the identity line, indicating perfect prediction. For seven of the other ten patients, the PP change of the predicted optimum combination was at least 75% of the maximum PP increase of the actual optimum combination. Only three of the Pacing Responders_{PP} had a predicted optimum combination with a

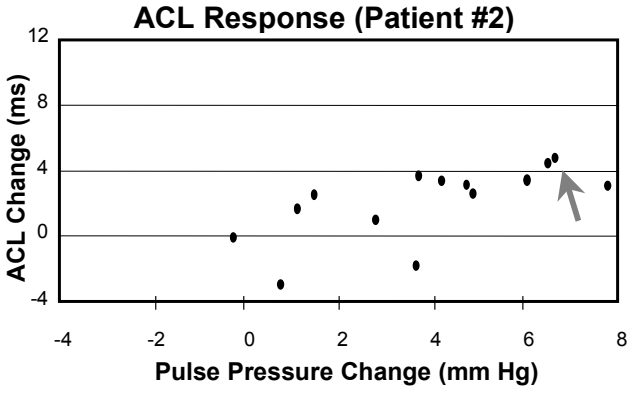

Fig. 1. *Identification of the optimum pacing combination for patient #2. Each point represents the average of one set of 5 trials at one particular combination of pacing site and AV delay. The arrow identifies the pacing combination that produces the maximum ACL increase. This combination is predicted to yield the maximum PP increase.*

PP change less than 75% of the maximum PP increase, with the worst case being 50% of maximum. Thus, for all Pacing $Responder_{PP}$ patients, the ACL algorithm predicted a pacing combination that improved PP. Moreover, for 85% of these patients, the ACL algorithm predicted pacing combinations at or near optimum. To quantify the effectiveness of the ACL optimization algorithm, the linear regression between the PP of the predicted and the actual optimum combinations was calculated for the Pacing $Responders_{PP}$ (dotted regression line, $R^2 = 0.90$, $P < .0001$).

2) A group of 6 patients (21%) where pacing therapy had little or no effect (maximum PP increase less than 5%). These patients (open circles) are both Pacing $Non\text{-}Responders_{PP}$ (gold standard) and Pacing $Non\text{-}Responders_{QRS}$. Pacing therapy improved PP for two patients (on identity line), had little or no effect for two patients (just above the x-axis), and worsened PP for two patients (below x-axis).

3) A group of 3 patients (10%) (circles with a dot in the middle) who were Pacing $Non\text{-}Responders_{PP}$ (gold standard) but who were identified as Pacing $Responders_{QRS}$. Pacing therapy had little or no effect on PP for two and a worsening of PP for the third.

The linear regression between the PP of the ACL predicted and the actual optimum combinations was calculated for the Pacing $Responders_{QRS}$ (filled circles and open circles with a dot in the middle; solid regression line, $R^2 = 0.78$, $P < .0001$)

IV. Discussion

Numerous studies have demonstrated that CRT can improve hemodynamics acutely in CHF patients. Acute hemodynamic improvement is typically documented by invasive pressure measurements, such as aortic pulse pressure, or by less invasive but time consuming methods such as echocardiography. In this analysis, we have developed an algorithm that relies solely on atrial electrical signals already available in any standard dual chamber pacemaker. By carefully measuring beat-to-beat changes in atrial cycle length during resynchronization therapy, we hypothesized that optimal settings for pacing site and AV delay could be inferred using the intrinsic baroreflex response of the patient. Therefore, we developed an algorithm to determine the combination of pacing parameters that yielded the greatest increase of ACL during resynchronization therapy.

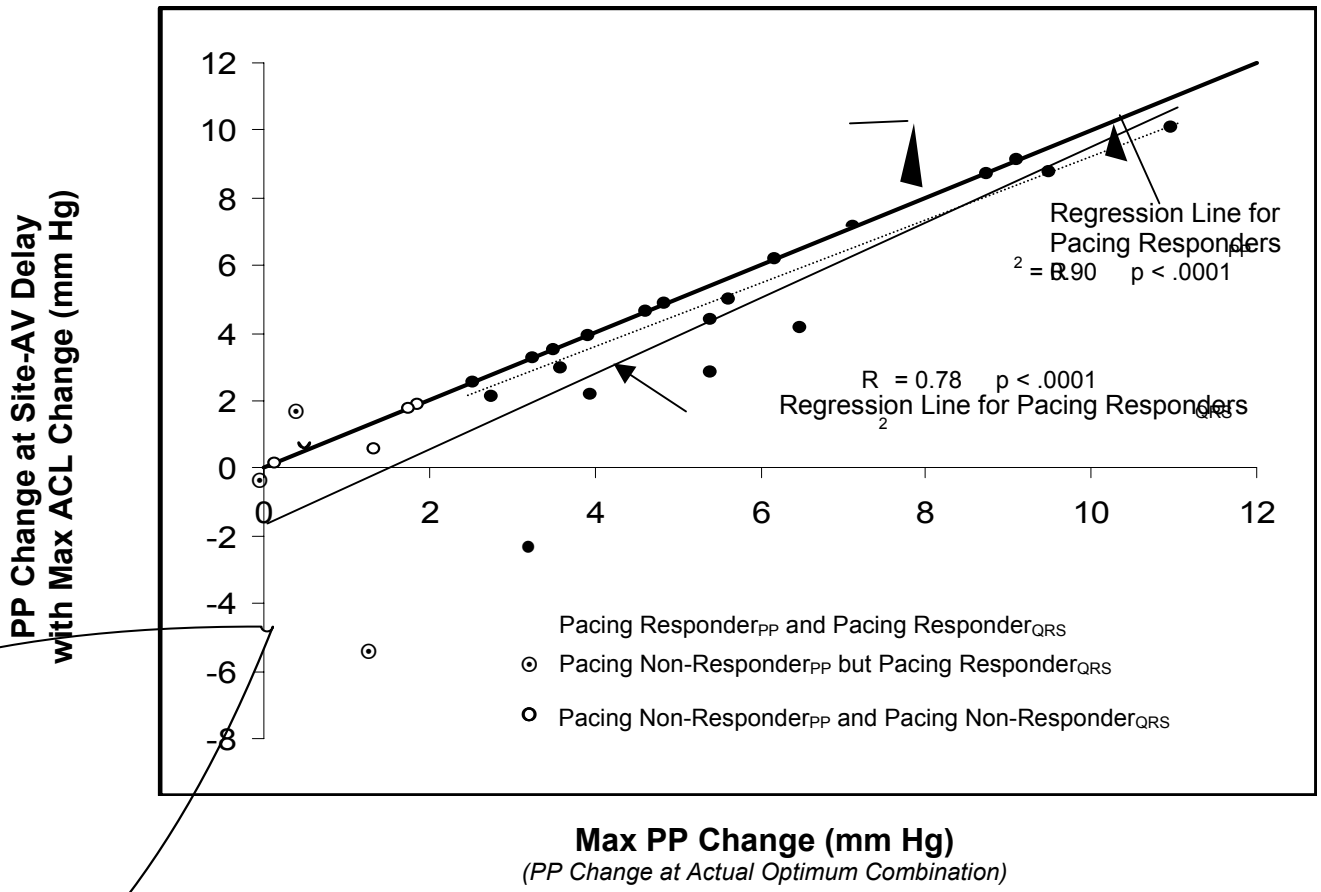

Fig. 2. *Effectiveness of the ACL optimization algorithm: comparison of the PP change from the predicted vs. actua*

optimum pacing combination, for each individual patient. Regressions were performed for two groups: patients whose PP increase during pacing was ≥ 5% of intrinsic (Pacing $Responders_{PP}$, denoted by filled circles; regression denoted by dotted line), and patients whose QRS width was ≥ 150 ms (Pacing $Responders_{QRS}$, composed of the filled circles plus the circles with dots in the middle; regression denoted by solid line).

For the 29 patients with atrial electrogram signals suitable to determine the ACL, the algorithm performance was acceptable. Of the 20 patients that had a documented (i.e. invasive) PP response, the ACL algorithm always recommended a combination of pacing site and AV delay that yielded an improvement in PP. Importantly, for 85% of these patients, ACL recommended settings that yielded 75% of the maximum possible hemodynamic response. These results suggest that in patients with conduction delay and CHF the baroreflex control over sinus rhythm remains functional and may be useful as a sensor of acute, transient hemodynamic response to resynchronization therapy. If these data can be reproduced in a large prospective study, then it may obviate the need for invasive optimization with pressure catheters or cumbersome optimization protocols that require echocardiography.

V. Conclusion

In this retrospective study, an algorithm was developed to assess changes in atrial cycle length based on the normal baroreceptor reflex. The ACL algorithm provides a physiologically-relevant method for the optimization and programming of cardiac resynchronization therapy in patients with CHF and conduction delay. The algorithm performed favorably, predicting optimal or near-optimal hemodynamic settings in the majority of patients.

The ACL optimization algorithm offers two distinct clinical advantages. First, it allows physicians to optimize pacing therapy for PP increase without using an invasive PP sensor. Second, the ACL algorithm allows physicians to test many combinations of pacing site and AV delay rapidly by utilizing transient rather than steady-state measurements. Additional research to prospectively evaluate the performance of the ACL algorithm in human subjects seems warranted.

VI. Limitations

The limitations of the ACL algorithm are that it will not work for patients who have frequent premature atrial or ventricular contractions, or who do not have normal sinus rhythm. The ACL algorithm does not predict the value of the maximum PP increase but predicts which tested combination of pacing site and AV delay has the maximum PP increase. The ACL algorithm does not predict which patients will respond to pacing and which will not; rather, the algorithm is applied to patients who have been pre-selected as pacing responders. In this research study, pacing responders were selected as those patients where pacing therapy produced at least a 5% increase in PP over intrinsic baseline for at least one pacing combination (Pacing Responders$_{PP}$). In a clinical setting, the physician will need to pre-select patients likely to be pacing responders based on patient characteristics (e.g., QRS width). The outcome of several large clinical trials of CRT may provide data for stratifying patients as responders/non-responders.

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